FAST TRACK

Drug treatments for covid-19: living systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE
To compare the effects of treatments for coronavirus disease 2019 (covid-19).

DESIGN
Living systematic review and network meta-analysis.

DATA SOURCES
US Centers for Disease Control and Prevention COVID-19 Research Articles Downloadable Database, which includes 25 electronic databases and six additional Chinese databases to 20 July 2020.

STUDY SELECTION
Randomised clinical trials in which people with suspected, probable, or confirmed covid-19 were randomised to drug treatment or to standard care or placebo. Pairs of reviewers independently screened potentially eligible articles.

METHODS
After duplicate data abstraction, a bayesian random effects network meta-analysis was conducted. Risk of bias of the included studies was assessed using a modification of the Cochrane risk of bias 2.0 tool, and the certainty of the evidence using the grading of recommendations assessment, development and evaluation (GRADE) approach. For each outcome, interventions were classified in groups from the most to the least beneficial or harmful following GRADE guidance.

RESULTS
23 randomised controlled trials were included in the analysis performed on 26 June 2020. The certainty of the evidence for most comparisons was very low because of risk of bias (lack of blinding) and serious imprecision. Glucocorticoids were the only intervention with evidence for a reduction in death compared with standard care (risk difference 37 fewer per 1000 patients, 95% credible interval 63 fewer to 11 fewer, moderate certainty) and mechanical ventilation (31 fewer per 1000 patients, 47 fewer to 9 fewer, moderate certainty). These estimates are based on direct evidence; network estimates for glucocorticoids compared with standard care were less precise because of network heterogeneity. Three drugs might reduce symptom duration compared with standard care: hydroxychloroquine (mean difference −4.5 days, low certainty), remdesivir (−2.6 days, moderate certainty), and lopinavir-ritonavir (−1.2 days, low certainty). Hydroxychloroquine might increase the risk of adverse events compared with the other interventions, and remdesivir probably does not substantially increase the risk of adverse effects leading to drug discontinuation. No other interventions included enough patients to meaningfully interpret adverse effects leading to drug discontinuation.

CONCLUSION
Glucocorticoids probably reduce mortality and mechanical ventilation in patients with covid-19 compared with standard care. The effectiveness of most interventions is uncertain because most of the randomised controlled trials so far have been small and have important study limitations.

SYSTEMATIC REVIEW REGISTRATION
This review was not registered. The protocol is included as a supplement.

READERS' NOTE
This article is a living systematic review that will be updated to reflect emerging evidence. Updates may

WHAT IS ALREADY KNOWN ON THIS TOPIC

Despite huge efforts to identify effective drug interventions for coronavirus disease 2019 (covid-19), evidence for effective treatment remains limited

WHAT THIS STUDY ADDS

This living systematic review and network meta-analysis provides a comprehensive overview and assessment of the evidence published as of 20 July 2020 and will be updated periodically

The certainty of the evidence for most interventions tested thus far is low or very low

In patients with severe covid-19, glucocorticoids probably decrease mortality and mechanical ventilation

Hydroxychloroquine, lopinavir-ritonavir, and remdesivir might reduce the time to symptom resolution

occur for up to two years from the date of original publication.

Introduction

As of 24 July 2020, more than 15.6 million people have been infected with severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (covid-19); of these, 636 000 have died.[1] Despite huge efforts to identify effective interventions for the prevention and treatment of covid-19, which have resulted in almost 1800 trials completed or underway,[2] evidence for effective treatment remains limited.

Faced with the pressures of a global pandemic, healthcare workers around the world are prescribing drugs off-label for which there is only very low quality evidence. The result—and this certainly seems to be the case for the well publicised example of hydroxychloroquine—might be of no benefit but of appreciable harm. Timely evidence summaries and associated guidelines could ameliorate the problem.[3] Clinicians, patients, guideline bodies, and government agencies are also facing the challenges of interpreting the results from trials that are being published at a rate never encountered previously. This environment makes it necessary to produce well developed summaries that distinguish more trustworthy evidence from less trustworthy evidence.

Living systematic reviews and network meta-analyses deal with the main limitation of traditional reviews—that of providing an overview of the relevant evidence only at a specific time.[4] This is crucial in the context of covid-19, in which the best evidence is constantly changing. The ability of a living network meta-analysis to present a complete, broad, and updated view of the evidence makes it ideal to inform the development of practice recommendations. Network meta-analysis, rather than pairwise meta-analysis, provides useful information about the comparative effectiveness of treatments that have not been tested head to head. The lack of such direct comparisons is certain to limit inferences in the covid-19 setting. Moreover, the incorporation of indirect evidence can strengthen evidence in comparisons that were tested head to head.[5]

In this living systematic review and network meta-analysis we compare the effects of drug treatments for covid-19. This review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and *The BMJ*. Our living systematic review and network meta-analysis will directly inform *BMJ* Rapid Recommendations[6] on covid-19 treatments, initiated to provide trustworthy, actionable, and living guidance to clinicians and patients soon after new and potentially practice-changing evidence becomes available. This systematic review informs a *BMJ* Rapid Recommendation (box 1).

Methods

A protocol provides the detailed methods of this systematic review, including all updates (see

> **Box 1: Linked resources in this *BMJ* Rapid Recommendations cluster**
> - Rochwerg B, Agarwal A, Zeng L, et al. Remdesivir for severe covid-19: a clinical practice guideline. *BMJ* 2020;370:m2924
>   - Summary of the results from the Rapid Recommendation process
> - Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020;370:m2980, doi:10.1136/bmj.m2980
>   - Review and network meta-analysis of all available randomised trials that assessed drug treatments for covid-19
> - MAGICapp (https://app.magicapp.org/#/guideline/j1W7rn)
>   - Expanded version of the methods, processes, and results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

supplementary file). We report this living systematic review following the guidelines of the preferred reporting items for systematic reviews and meta-Analyses (PRISMA) checklist for network meta-analyses.[7] A living systematic review is a cumulative synthesis that is updated regularly as new evidence becomes available.[8] The linked *BMJ* Rapid Recommendations guideline panels approved all decisions relevant to data synthesis.

Eligibility criteria

We included randomised clinical trials in people with suspected, probable, or confirmed covid-19 that compared drugs for treatment against one another or against no intervention, placebo, or standard care. We included trials regardless of publication status (peer reviewed, in press, or preprint) or language. No restrictions were applied based on severity of illness or setting and we included trials of Chinese medicines if the drug comprised one or more specific molecules with a defined molecular weight dosing.

We excluded randomised controlled trials evaluating vaccination, blood products, nutrition, traditional Chinese herbal medicines that include more than one molecule or a molecule without specific molecular weighted dosing, and non-drug supportive care interventions. Trials including patients with covid-19 that evaluated these interventions were identified and categorised separately.

Information sources

We perform daily searches from Monday to Friday in the US Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database for eligible studies—the most comprehensive database of covid-19 research articles.[9] The database includes 25 bibliographic and grey literature sources: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus,

Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO covid-19 website, CDC covid-19 website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints).

The daily searches are designed to match the update schedule of the database and to capture eligible studies the day of or the day after publication. To identify randomised controlled trials, we filtered the results from the CDC's database through a validated and highly sensitive machine learning model.[10] We tracked preprints of randomised controlled trials until publication and updated data to match that in the peer reviewed publication when discrepant and reconciled corrections and retractions existed.

In addition, we search six Chinese databases every two weeks basis: Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints). We adapted the search terms for covid-19 developed by the CDC to the Chinese language. For the Chinese literature search, we also included search terms for randomised trials. The supplementary file includes the Chinese literature search strategy.

We monitor living evidence retrieval services on an ongoing basis. These included the Living Overview of the Evidence (L-OVE) COVID-19 Repository by the Epistemonikos Foundation and the Systematic and Living Map on COVID-19 Evidence by the Norwegian Institute of Public Health, in collaboration with the Cochrane Canada Centre at McMaster University.[11]

We searched all English information sources from 1 December 2019 to 20 July 2020, and the Chinese literature from conception of the databases to 20 July 2020.

Study selection

Using a systematic review software, Covidence,[12] pairs of reviewers, following training and calibration exercises, independently screened all titles and abstracts, followed by full texts of trials that were identified as potentially eligible. A third reviewer adjudicated conflicts.

Data collection

For each eligible trial, pairs of reviewers, following training and calibration exercises, extracted data independently using a standardised, pilot tested data extraction form. Reviewers collected information on trial characteristics (trial registration, publication status, study status, design), patient characteristics (country, age, sex, smoking habits, comorbidities, setting and type of care, and severity of covid-19 symptoms for studies of treatment), and outcomes of interest (means or medians and measures of variability for continuous outcomes and the number of participants analysed and the number of participants who experienced an event for dichotomous outcomes).

Reviewers resolved discrepancies by discussion and, when necessary, with adjudication by a third party. We updated the data collected from included studies when they were published as a preprint and as soon as the peer review publication became available in studies initially included as preprints.

Outcomes of interest were selected based on importance to patients and were informed by clinical expertise in the systematic review team and in the linked guideline panel responsible for the *BMJ* Rapid Recommendations.[13] The panel includes unconflicted clinical experts, recruited to ensure global representation, and patient-partners. Outcomes were rated from 1 to 9 based on importance to individual patients (9 being most important), and we included any outcome rated 7 or higher by any panel member. Selected outcomes included mortality (closest to 90 days), mechanical ventilation (total number of patients, over 90 days), adverse events leading to discontinuation (within 28 days), viral clearance (closest to 7 days, 3 days either way), duration of hospital stay, intensive care unit (ICU) length of stay, time to symptom resolution or clinical improvement, and time to viral clearance. Viral clearance at seven days and time to viral clearance were included because both may be surrogates for transmissibility, although this is uncertain.[14]

Because of the inconsistent reporting observed across trials, in the updates we will use a hierarchy for the outcome mechanical ventilation in which we will include information from the total number of patients who received ventilation over a period if available (as done for this analysis), but we will also include the number at the time when most of the patients were mechanically ventilated if that is the only way in which this outcome is reported.

Risk of bias within individual studies

For each eligible trial, reviewers, following training and calibration exercises, used a revision of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2.0)[15] to rate trials as either at i) low risk of bias, ii) some concerns—probably low risk of bias, iii) some concerns—probably high risk of bias, or iv) high risk of bias, across the following domains: bias arising from the randomisation process; bias owing to departures from the intended intervention; bias from missing outcome data; bias in measurement of the outcome; bias in selection of the reported results, including deviations from the registered protocol; and bias arising from early termination for benefit. We rated trials at high risk of bias overall if one or more domains were rated as some concerns—probably high risk of bias or as high risk of bias and as low risk of bias if all domains were rated as some concerns—probably low risk of bias or low risk of bias. Reviewers resolved discrepancies by discussion and, when not possible, with adjudication by a third party.

Data synthesis

We conducted the network meta-analysis using a bayesian framework.[16] In this report, we conducted a

network meta-analysis of drug treatments for covid-19 that included all patients, regardless of severity of disease.

Summary measures

We summarised the effect of interventions on dichotomous outcomes using the odds ratio and corresponding 95% credible interval. For continuous outcomes, we used the mean difference and corresponding 95% credible interval in days for ICU length of stay and duration of mechanical ventilation because we expected similar durations across randomised controlled trials. For time to symptom resolution and length of hospital stay, we first performed the analyses using the relative effect measure ratio of means and corresponding 95% credible interval before calculating the mean difference in days because we expected substantial variation between studies.[17]

Treatment nodes

Treatments were grouped into common nodes based on molecule and not on dose or duration. For intervention arms with more than one drug, we created a separate node and included drugs from the same class within the same node. Chloroquine and hydroxychloroquine were included in the same node for covid-19 specific effects and separated for disease independent adverse effects. We drew network plots using the *networkplot* command of Stata version 15.1 (StataCorp, College Station, TX), with thickness of lines between nodes and size of the nodes based on the number of studies.[18]

Statistical analysis

For most outcomes, we conducted random effects network meta-analyses using a bayesian framework with the same priors for the variance and effect parameters.[16] For networks with particularly sparse outcomes, we conducted fixed effect network meta-analysis.[19] We used a plausible prior for variance parameter and a uniform prior for the effect parameter suggested in a previous study based on empirical data.[20] For all analyses, we used three Markov chains with 100 000 iterations after an initial burn-in of 10 000 and a thinning of 10. We used node splitting models to assess local incoherence and to obtain indirect estimates.[21] All network meta-analyses were performed using the *gemtc* package of R version 4.0.0 (RStudio, Boston, MA).[22]

Some treatment nodes with few total participants and few total events resulted in highly implausible and extremely imprecise effect estimates. We therefore decided to include only treatments that enrolled at least 100 patients or had at least 20 events. For this iteration, the analyses included treatment nodes with fewer than 100 patients and 20 events, but the results are not reported.

Certainty of the evidence

We assessed the certainty of evidence using the grading of recommendations assessment, development and evaluation (GRADE) approach for network meta-analysis.[5 23 24] Two people with experience in using GRADE rated each domain for each comparison separately and resolved discrepancies by consensus. We rated the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence (difference between direct and indirect effects), and imprecision.[24] Judgments of imprecision for this systematic review were made using a minimally contextualised approach, with a null effect as the threshold of importance.[25] The minimally contextualised approach considers only whether credible intervals include the null effect and thus does not consider whether plausible effects, captured by credible intervals, include both important and trivial effects.[25] We created GRADE evidence summaries (Summary of Findings tables) in the MAGIC Authoring and publication platform (www.magicapp.org) to provide user friendly formats for clinicians and patients and to allow re-use in the context of clinical practice guidelines for covid-19.

Interpretation of results

To facilitate interpretation of the results, we calculated absolute effects for outcomes in which the summary measure was an odds ratio or ratio of means. For the outcomes mortality and mechanical ventilation, we used baseline risks from the International Severe Acute Respiratory and Emerging Infection COVID-19 database.[26] For all other outcomes, we used the median from all studies in which participants received standard of care to calculate the baseline risk for each outcome, with each study weighed equally. We calculated absolute effects using the transitive risks model[27] using *R2jags* package in R.[28]

For each outcome, we classified treatments in groups from the most to the least effective using the minimally contextualised framework, which focuses on the treatment effect estimates and the certainty of the evidence.[29]

Subgroup and sensitivity analysis

When a comparison was dominated by a single study (defined as >90% contribution in fixed effects), we conducted our primary analysis with a fixed effects model for that comparison.[19] We planned to perform subgroup analyses of preprints versus peer reviewed studies and high versus low risk of bias. We will perform additional subgroup analyses in the future if directed by the linked independent Rapid Recommendation guideline panels; in this case there was no such direction.

Patient and public involvement

Patients were involved in the interpretation of results and the generation of parallel recommendations, as part of the *BMJ* Rapid Recommendations initiative.

Results

After screening 7285 titles and abstracts and 122 full texts, 32 unique randomised controlled trials were

identified that evaluated drug treatments as of 20 July 2020 (fig 1).[30-51] Searches of living evidence retrieval services identified one additional eligible randomised controlled trial.[52] Eighteen randomised controlled trials have been published in peer reviewed journals, and 14 only as preprints. Most of the trials were registered (30/32; 94%), published in English (30/32; 94%), and evaluated treatment in patients admitted to hospital with covid-19 (28/32; 88%). Just over one half of the trials were conducted in China (18/32; 56%). Of the 32 included drug trials, six evaluated treatment against active comparators, 18 evaluated treatment against standard care or placebo, and two evaluated different durations or doses of the same treatment. Our analyses were performed on 26 June 2020 and include 20 randomised controlled trials.[31 34-39 41-50] Table 1 presents the characteristics of the included studies. Additional study characteristics, outcome data, and risk of bias assessments for each study are available in the supplementary file.

Several randomised controlled trials were not included in the analysis: two trials that evaluated different durations of the same drug, because both arms would have been classified within the same treatment node[32 40]; one trial that compared lincomycin with azithromycin,[55] because neither arm was connected to the network; 10 trials that compared technetium 99m-methyl diphosphonate (^{99}mTC-MDP),[62] azvudine,[63] colchicine,[64] febuxostat,[65] hydroxychloroquine,[66-70] and hydroxychloroquine with darunavir-cobicistat[68 69] because they were identified, or the data were available, after the analysis was completed. Table 2 describes the randomised controlled trials that were identified after the data analysis and that will be included in the next update.

Of the randomised controlled trials included in the analyses, two did not have publicly accessible protocols or registrations.[55 61] Of the trials with publicly accessible protocols or registrations, 16 reported results for one or more of our outcomes of interest that were not prespecified in protocols or registrations. No other discrepancies between the reporting of our outcomes of interest in trial reports and protocols or registrations were noted. One trial did not report outcomes in the groups as randomised; the authors shared outcome data with us in the groups as randomised.[49]

Five studies were initially posted as preprints and subsequently published after peer review.[32 39 44 48 51 54 56-59] In one study, mortality was not reported in the preprint but was reported in the peer reviewed paper.[44 59] A trial that compared dexamethasone with standard care was published as a preprint before our data analysis[48] and has since been published with additional events after peer review.[56] No substantive differences were found between the preprint and peer reviewed publications for the other three studies.

All analyses reached convergence based on trace plots and a Brooks-Gelman-Rubin statistic less than 1.05. Two randomised controlled trials that studied glucocorticoids differed substantially in size (the Randomised Evaluation of COVID-19 therapy (RECOVERY) trial enrolled 6425 patients[48] and GLUCOCOVID 63[49]), thus we performed a fixed effects analysis for the direct pairwise analysis for the outcomes that were reported in both of the trials (mortality and mechanical ventilation). This analysis was separate from the network meta-analyses, which was conducted with random effects. Owing to insufficient data, we did not conduct any of the subgroup or sensitivity analyses specified in the protocol (see supplementary file). For comparisons between treatments with at least 100 patients or 20 events, the effects were similar whether or not we included treatments with fewer patients and events in the network meta-analyses (see supplementary file).

Risk of bias in included studies
The supplementary material presents the assessment of risk of bias of the included studies for each outcome. Two studies were judged at low risk of bias in all domains.[31 45] All other studies had probably high or high risk of bias in the domains of randomisation or deviation from the intended interventions.

Effects of the interventions
The supplementary material presents the network plots depicting the interventions included in the network meta-analysis of each outcome. Figure 2 presents a summary of the effects of the interventions on the outcomes. The supplementary file also presents detailed relative and absolute effect estimates and certainty of the evidence for all comparisons and outcomes. No statistical incoherence was detected in any of the network meta-analyses.

Mortality
Fifteen randomised controlled trials including 8654 participants[31 34-37 39 41-46 48-50 71 72] reported mortality. The treatment nodes included in the network meta-analysis were glucocorticoids, hydroxychloroquine, lopinavir-ritonavir, remdesivir, umifenovir, and standard care. The network estimates did not reveal a convincing reduction for any of these interventions compared with standard care. The certainty of the evidence was low for the comparison between remdesivir and standard of care, and very low for all other comparisons (fig 2). For glucocorticoids, the direct estimate was more credible than the network estimate (moderate certainty versus very low certainty) because the direct estimate was more precise. The network estimate (relative risk), which considers heterogeneity of the entire network, was 0.84 (95% credible interval 0.52 to 1.36). The direct pairwise meta-analysis of two trials of glucocorticoids versus standard care[48 49] suggested a probable reduction in mortality with glucocorticoids (relative risk 0.88 (95% credible interval 0.80 to 0.97), risk difference 37 fewer per 1000 patients (95% credible interval 63 fewer to 11 fewer), moderate certainty for risk of bias).
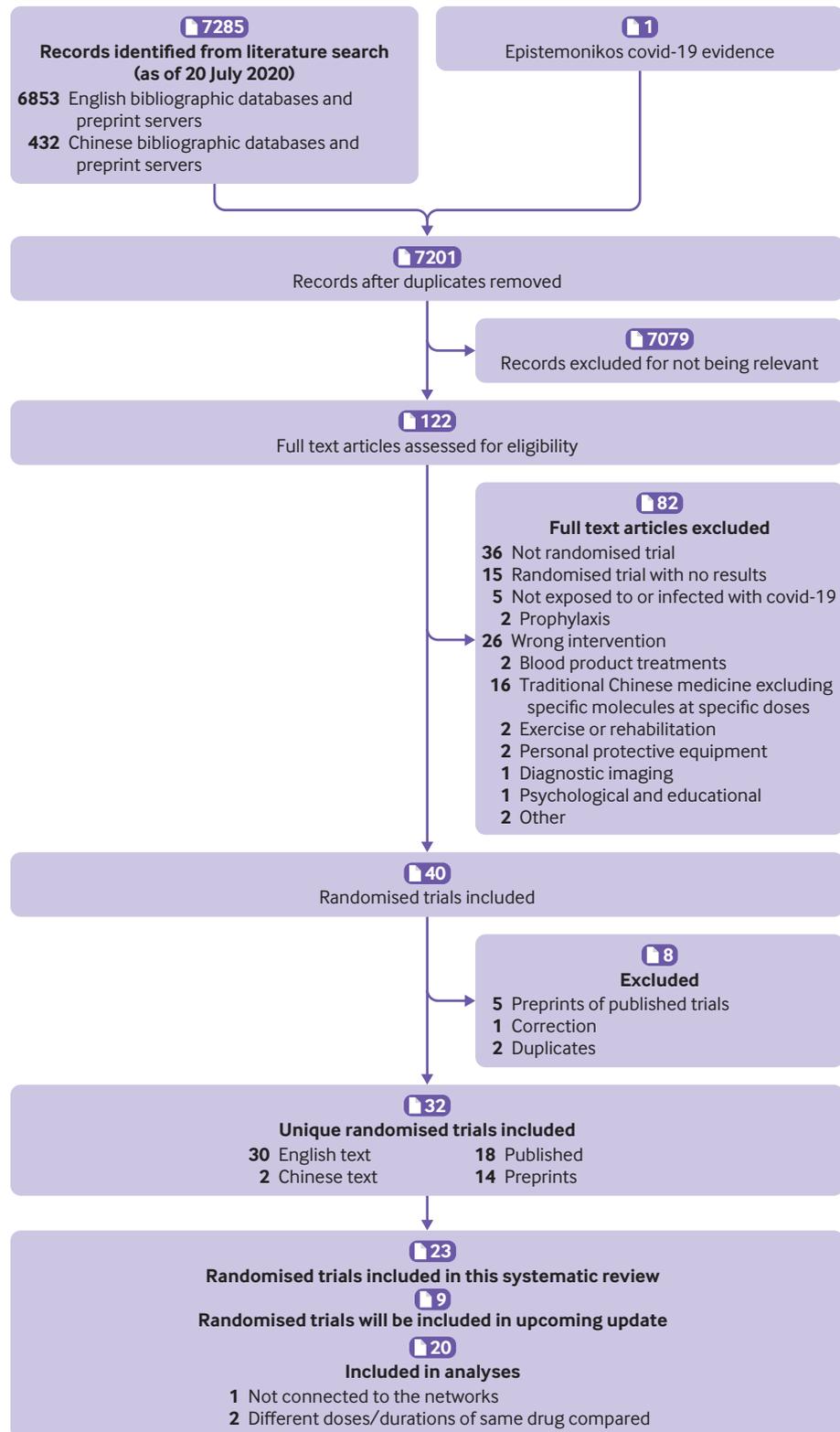
Fig 1 | Study selection

Mechanical ventilation

Eight randomised controlled trials that enrolled 6953 participants[31 34 35 39 41 42 45 48 49 71 72] reported mechanical ventilation in patients who were not receiving mechanical ventilation at baseline. The treatment nodes included in the network meta-analysis were glucocorticoids, remdesivir, and standard care (fig 2). The network estimate for glucocorticoids was very low certainty because of serious imprecision (relative risk 0.71, 95% credible interval 0.29 to 1.73). The direct pairwise meta-analysis for glucocorticoids versus standard care[48 49] resulted in higher certainty and

Table 1 | Study characteristics

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Beigel 2020; ACTT-1 [131]	Published, NCT04280705	1063	USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore	58.9	64.3	Inpatient; coronary artery disease (11.6%); congestive heart failure (5.0%); diabetes (29.7%); hypertension (49.6%); asthma (11.4%); chronic oxygen requirement (2.2%); chronic respiratory disease (7.6%)	Mild/moderate (11.3%); severe (88.7%)	44.1	Remdesivir (100 mg/day for 10 days); placebo	Mortality; mechanical ventilation; adverse effects leading to discontinuation; time to symptom or clinical improvement
Cao 2020; LOTUS China [34]	Published, ChiCTR2000029308	199	China	58.0	60.3	Inpatient; cerebrovascular disease (6.5%); diabetes (11.6%)	Severe (100%)	16.1	Lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation; viral clearance; duration of hospital stay; intensive care unit length of stay; duration of ventilation; time to symptom or clinical improvement
Cao 2020 [35]	Published, ChiCTR-OPN-2000029580	43	China	63.0	58.5	Inpatient; coronary artery disease (7.3%); diabetes (19.5%); hypertension (39.0%)	Severe (100%)	12.2	Ruxolitinib (5 mg twice daily); placebo	Mortality; mechanical ventilation; duration of hospital stay; duration of ventilation; time to symptom or clinical improvement; time to viral clearance
Chen 2020 [38]	Preprint, ChiCTR2000029559	62	China	44.7	46.8	Inpatient; NR	Mild/moderate (100%)	NR	Hydroxychloroquine (200 mg twice daily for 5 days); standard care	Adverse effects leading to discontinuation; time to symptom or clinical improvement
Chen 2020 [36]	Preprint, ChiCTR2000030254	240	China	NR	46.6	NR; diabetes (11.4%); hypertension (28.0%)	Mild/moderate (88.6%); severe (10.2%); critical (1.3%)	NR	Favipiravir (600 mg twice daily for 7 days); umifenovir (200 mg three times daily for 7 days)	Mortality; time to symptom or clinical improvement
Chen 2020 [37]	Preprint, ChiCTR2000029387	101	China	42.5	45.5	NR	Mild/moderate (100%)	NR	Ribavirin (400-600 mg three times daily for 14 days), interferon-alfa (5 mg twice daily for 14 days); lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days), interferon-alfa (5 mg twice daily for 14 days); ribavirin (400-600 mg three times daily for 14 days), lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days), interferon-alfa (5 mg twice daily for 14 days)	Mortality; viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Chen 2020 [53]	Published, NCT04261517	30	China	48.6	70.0	Inpatient; diabetes (6.7%); hypertension (26.7%); chronic obstructive pulmonary disease (3.3%)	Mild/moderate (100%)	NR	Hydroxychloroquine (400 mg/day for 5 days); standard care	Mortality; adverse events leading to discontinuation; viral clearance; time to symptom or clinical improvement; time to viral clearance
Chen 2020 [50]	Preprint, ChiCTR2000030054	48	China	46.9	45.8	Inpatient; diabetes (18.8%); hypertension (16.7%)	Mild/moderate (100%)	NR	Chloroquine (500 mg/day for 10 days); hydroxychloroquine (200 mg twice daily for 10 days); standard care	Mortality; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance

(Continued)

Table 1 | Continued

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Corral-Gudino 2020†; GLUCOCOVID[49]	Preprint, 2020-001934-37	63	Spain	69.8	61.9	Inpatient; heart disease (12.7%); diabetes (17.5%); hypertension (47.6%); respiratory condition (7.9%)	Critical (0%)	0	Methylprednisolone (40 mg twice daily for 3 days, then 20 mg twice daily for 3 days); standard care	Mortality; mechanical ventilation
Davoudi-Monfared 2020[39][54]	Preprint, IRCT20100228003449N28	92	Iran	57.8	53.1	Inpatient; cardiovascular disease (28.4%); diabetes (27.2%); hypertension (38.3%); asthma (1.2%); chronic obstructive pulmonary disease (1.2%)	Severe (100%)	29.6	Interferon beta-1a (44 µg/ml three times weekly for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay; duration of ventilation; time to symptom or clinical improvement
Goldman 2020*[40]	Published, NCT04292899	402	USA, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan	61.5	63.7	Inpatient; diabetes (22.7%); hypertension (49.9%); asthma (12.3%)	Severe (100%)	30.7	Remdesivir (100 mg/day for 5 days); remdesivir (100 mg/day for 10 days)	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; time to symptom or clinical improvement
Guvenmez 2020[55]	Published	24	Turkey	58.8	62.5	Inpatient; NR	NR	0	Lincomycin (600 mg twice daily for 5 days); azithromycin (250 mg/day for 5 days)	Viral clearance
Horby 2020; RECOVERY[48][56]	Preprint, NCT04381936	6425	UK	66.1	63.6	Inpatient; heart disease (27.3%); diabetes (24.1%); chronic lung disease (20.9%); tuberculosis (0.4%)	NR	15.7	Dexamethasone (6 mg/day for 10 days); standard care	Mortality; mechanical ventilation; duration of hospital stay
Huang 2020[52]	Published, ChiCTR2000029542	22	China	44.0	59.1	Inpatient; cerebrovascular disease (4.5%); diabetes (9.1%); hypertension (18.2%)	Mild/moderate (63.6%); severe (36.4%)	NR	Chloroquine (500 mg twice daily for 10 days); lopinavir-ritonavir (400 mg and 100 mg twice daily for 10 days)	Viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Hung 2020[41]	Published, NCT04276688	127	China	51.3	53.5	Inpatient; coronary artery disease (7.9%); cerebrovascular disease (1.6%); diabetes (13.4%); hypertension (28.4%); obstructive sleep apnoea (1.6%); tuberculosis (1.6%)	Mild/moderate (100%)	0	Lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days), ribavarin (400 mg twice daily for 14 days), interferon beta-1b (1-3 mL every other day); lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days)	Mortality; mechanical ventilation; adverse effects leading to discontinuation; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Li 2020; ELACOI[51][57]	Published, NCT04252885	86	China	49.4	46.5	Inpatient; cardiovascular disease (2.3%); diabetes (2.3%); hypertension (10.5%)	Mild/moderate (100%)	0	Lopinavir-ritonavir (200 mg and 50 mg twice daily for 7 to 14 days); umifenovir (200 mg three times daily for 7 to 14 days); standard care	Mortality; adverse effects leading to discontinuation; viral clearance; time to viral clearance
Lou 2020[42]	Preprint, ChiCTR2000029544	30	China	52.5	72.4	Inpatient; cardiovascular disease (13.8%); diabetes (6.9%); hypertension (20.7%)	NR	0	Baloxavir marboxil (80 mg/day for up to 3 doses on days 1, 4, and 7); favipiravir (600 mg three times daily for 14 days); standard care	Mortality; mechanical ventilation; viral clearance; time to symptom or clinical improvement; time to viral clearance

(Continued)

Table 1 | Continued

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Silva Borba 2020*; CloroCOVID-19[32 58]	Published, NCT04323527	81	Brazil	51.1	75.3	Inpatient; intensive care (45.7%); cardiovascular disease (9.1%); diabetes (25.5%); hypertension (45.5%); asthma (7.4%); tuberculosis (3.6%)	Severe (100%)	NR	Chloroquine (600 mg twice daily for 10 days); chloroquine (450 mg/day for 5 days)	Mortality
Tang 2020[44 59]	Published, ChiCTR2000029868	150	China	46.1	55.0	Inpatient; diabetes (14.0%); hypertension (6.0%)	Mild/moderate (99.0%); severe (1.0%)	NR	Hydroxychloroquine (800 mg/day for 14 to 21 days); standard care	Mortality; adverse effects leading to discontinuation; viral clearance; time to symptom or clinical improvement; time to viral clearance
Wang 2020[45]	Published, NCT04257656	237	China	65.0	59.3	Inpatient; cardiovascular disease (7.2%); diabetes (23.7%); hypertension (43.2%)	Severe (100%)	16.1	Remdesivir (100 mg/day for 10 days); placebo	Mortality; mechanical ventilation; adverse events leading to discontinuation; viral clearance; duration of hospital stay; duration of ventilation; time to symptom or clinical improvement
Zheng 2020[47]	Preprint, ChiCTR2000029496	89	China	46.7	47.2	Inpatient	Mild/moderate (94.4%); severe (5.6%)	NR	Novaferon (20 µg twice daily for 7 to 10 days); novaferon, lopinavir-ritonavir (200 mg and 50 mg twice daily for 7 to 10 days); lopinavir-ritonavir (200 mg and 50 mg twice daily for 7 to 10 days)	Adverse events leading to discontinuation; viral clearance; time to viral clearance
Zhong 2020[60]	Preprint, ChiCTR2000029851	17	China	63.0	76.5	Inpatient; cardiovascular disease (5.9%); diabetes (23.5%); hypertension (47.1%)	Critical (100%)	94.1	Alpha lipoic acid (1200 mg/day for 7 days); placebo	Mortality; adverse events leading to discontinuation
Zhou 2020[61]	Published	104	China	52.1	57.7	Inpatient	Mild/moderate (100%)	NR	Diammonium glycyrrhizinate (150 mg three times daily for 14 days), lopinavir-ritonavir (500 mg twice daily for 14 days); lopinavir-ritonavir (500 mg twice daily for 14 days)	Adverse events leading to discontinuation

NR=not reported

*Not included in network meta-analysis.

†Not included in the current iteration of the network meta-analysis but will be included in the next iteration. Corral-Gudino et al 2020 was included in the pairwise meta-analysis of glucocorticoids.

‡This study was not included in the network meta-analyses because neither of the study drugs were studied in any other randomised trials.

Table 2 | Randomised trials identified after data analysis, which will be included in the next update

Study	Publication status, registration No	No of participants	Treatments
Davoodi 2020[65]	Published, IRCT2019072704434N1	60	Febuxostat; hydroxychloroquine
Deftereos 2020; GRECCO-19[64]	Published, NCT04326790	110	Colchicine; standard care
Horby 2020; RECOVERY[66]	Preprint, NCT04381936	4716	Hydroxychloroquine; standard care
Chen 2020[70]	Preprint, NCT04384380	33	Hydroxychloroquine; standard care
Yuan 2020[62]	Preprint, ChiCTR2000029431	21	99m-methyl diphosphonate (^{99}mTc-MDP); standard care
Skipper 2020[67]	Published, NCT04308668	491	Hydroxychloroquine; placebo
Mitjà 2020; BCN PEP-CoV-2[68]	Published, NCT04304053	353	Hydroxychloroquine; standard care
Mitjà 2020; BCN PEP-CoV-2[69]	Preprint, NCT04304053	352	Hydroxychloroquine; hydroxychloroquine, darunivir-cobicistat; standard care
Ren 2020[63]	Published, ChiCTR2000029853	20	Azvudine; standard care

	Mortality	Mechanical ventilation	Adverse events	Viral clearance	Duration of hospital stay	ICU length of stay	Duration of mechanical ventilation	Time to symptom resolution	Time to viral clearance
Standard care	330 per 1000	116 per 1000	15 per 1000	500 per 1000	7 days	10 days	10 days	19 days	8 days
Alpha lipoic acid									
Baloxavir marboxil									
Chloroquine*									
Gluco-corticoids	-37.35 (-62.88 to -11.24)†	-31.00 (-47.00 to -9.00)†							
Diammonium Glycyrrhizinate									
Favipiravir									
Hydroxy-chloroquine	-329.75 (-330.00 to 670.00)		985.06 (24.68 to 985.10)	82.50 (-342.90 to 413.67)				-4.53 (-5.98 to -2.99)	-0.46 (-3.00 to 3.47)
Interferon beta-1a									
Lopinavir-ritonavir	-71.13 (-196.58 to 109.37)			-238.91 (-478.10 to 234.68)	-1.42 (-3.03 to 0.02)			-1.22 (-2.00 to -0.37)	-0.23 (-3.08 to 4.24)
Novaferon									
Novaferon, lopinavir-ritonavir									
Remdesivir	-85.01 (-164.24 to 29.28)	-24.00 (-70.00 to 52.00)	3.84 (-7.22 to 41.59)	11.19 (-468.95 to 471.78)	0.35 (-3.82 to 4.53)		-5.26 (-15.20 to 4.96)	-2.58 (-4.32 to -0.54)	
Ribavirin									
Ribavirin, interferon beta-1b									
Ribavirin, lopinavir-ritonavir									
Ruxolitinib									
Umifenovir	-330.00 (-330.00 to 670.00)								

	Most beneficial	Intermediate benefit	Not different from SC	Harmful	Insufficient data
High/moderate certainty					<100 patients
Low/very low certainty					No data

* Chloroquine was treated as a separate node for adverse events, and was combined with hydroxychloroquine for all other outcomes
† The best estimate of effect was obtained from direct evidence

Fig 2 | Summary of effects of interventions on outcomes. Numbers are absolute risk differences (95% credible intervals) per 1000 patients or mean differences (95% credible intervals) in days compared with standard care (SC). Empty cells represent no evidence for the specific intervention. Grey cells represent fewer than 100 patients randomised to the intervention for the outcome. ICU=intensive care unit

suggested a probable reduction with glucocorticoids versus standard care (relative risk 0.74 (95% credible interval 0.59 to 0.93), risk difference 30 fewer per 1000 patients (95% credible interval 48 fewer to 8 fewer), moderate certainty for risk of bias).

Adverse events leading to discontinuation
Eleven randomised controlled trials including 1875 participants[31 38 39 41 43-47 50 72] reported adverse effects leading to discontinuation of the study drug. The treatment nodes included in the network meta-analysis were hydroxychloroquine, remdesivir, and standard care. Moderate certainty evidence showed that remdesivir did not result in any additional harm beyond standard care and low certainty evidence showed that hydroxychloroquine increased the risk of adverse events compared with standard care (fig 2).

Viral clearance at 7 days (3 days either way)
All 10 randomised controlled trials that cumulatively enrolled 856 participants[34 37 42 44-47 50 52 72] measured viral clearance with polymerase chain reaction cut-off points. The treatment nodes included in the network meta-analysis were hydroxychloroquine, lopinavir-ritonavir, remdesivir, and standard care. We did not find any convincing evidence that any of the interventions increased the rate of viral clearance (fig 2). The certainty of the evidence was low for remdesivir compared with standard care, and very low for all other comparisons.

Duration of hospital stay
Eight randomised controlled trials including 855 participants[34 35 37 39 41 45 48 50 52 72] reported duration of hospital stay. The treatment nodes included in the network meta-analysis were lopinavir-ritonavir, remdesivir, and standard care. Patients who received lopinavir-ritonavir had fewer days of hospital stay than patients who received standard care, but the effect estimate included no difference (risk difference −1.42 days, 95% credible interval −3.03 to 0.02, low certainty; fig 2). Remdesivir did not seem to reduce the duration of hospital stay (low certainty).

ICU length of stay
Two randomised controlled trials including 280 participants reported length of ICU stay.[34 39] The treatments evaluated were lopinavir-ritonavir and interferon beta-1 versus standard care. Standard care was the only treatment node with at least 100 patients and therefore no analyses were performed for this outcome.

Duration of mechanical ventilation
Three randomised controlled trials including 557 participants[34 39 45] reported duration of mechanical ventilation. The treatment nodes included in the meta-analysis were remdesivir and standard care. Moderate certainty evidence showed that remdesivir reduces the duration of mechanical ventilation compared with standard care (mean difference −5.15 days, 95% credible interval −8.28 to −2.02; fig 2).

Time to symptom resolution
Thirteen randomised controlled trials including 2282 participants[31 34-39 41 42 44 45 50 52 72] reported time to symptom resolution. At least 100 patients received hydroxychloroquine, lopinavir-ritonavir, remdesivir, and standard care. Patients who received remdesivir (mean difference −2.58 days, 95% credible interval −4.32 to −0.54, moderate certainty), hydroxychloroquine (−4.53 days, −5.98 to −2.99, low certainty), and lopinavir-ritonavir (−1.22 days, −2.00 to −0.37, low certainty) had a shorter symptom duration than patients who received standard care.

Time to viral clearance
Ten randomised controlled trials including 684 participants[35 37 41 42 44 46 47 50 52 72] found no convincing evidence that any of the interventions reduced the time to viral clearance. At least 100 patients received hydroxychloroquine, lopinavir-ritonavir, remdesivir, and standard care. The certainty of the evidence was very low for all comparisons (fig 2).

Discussion
This living systematic review and network meta-analysis provides a comprehensive overview of the evidence for drug treatments of covid-19 up to 20 July 2020. The certainty of the evidence for most of the comparisons was very low. The only intervention that probably reduces mortality and mechanical ventilation is glucocorticoids, a result driven entirely by the RECOVERY trial.[48] Remdesivir is the only intervention in which moderate certainty exists supporting benefits for both time to symptom resolution and duration of mechanical ventilation, but it remains uncertain whether remdesivir has any effect on mortality and other outcomes important to patients. Remdesivir was the only intervention where all the data came from randomised controlled trials sponsored by a pharmaceutical company. Direct evidence from randomised controlled trials in patients with covid-19 has so far provided little definitive evidence about adverse effects for most interventions.

Hydroxychloroquine might increase the risk of adverse events leading to drug discontinuation compared with the other interventions. Notably, this iteration of the living network meta-analysis did not include four recently published randomised controlled trials on hydroxychloroquine compared with standard care.[66-68 73] RECOVERY, the largest randomised controlled trial on hydroxychloroquine, suggests that hydroxychloroquine might not reduce mortality and might increase length of hospital stay.[66] These data will be included in the next update. No convincing evidence was found that the other interventions resulted in benefits or harms compared with standard of care.

Strengths and limitations of this review
Our search strategy and eligibility criteria were comprehensive, without restrictions on language of publication, and provide an overview of the current

evidence. To ensure expertise in all areas, our team is composed of clinical and methods experts who have undergone training and calibration exercises for all stages of the review process. To minimise problems with counterintuitive results, in our data analysis plan we anticipated challenges that arise in network meta-analysis when data are sparse.[19] We assessed the certainty of the evidence using the GRADE approach and interpreted the results considering absolute effects. Many of the results for comparisons with sparse data were uninformative and were sometimes implausible. For that reason, we decided to report evidence on treatments for which at least 100 people were randomised. In the future, when more data from more treatments are available, our classification of interventions from the most to the least effective will facilitate clear interpretation of results.

The main limitation of the systematic review is the very low quality of the evidence as a result of the sparse data currently available. As the many ongoing trials are completed, we anticipate that the effect estimates will quickly become both plausible and informative as the quality of the evidence increases. Only two studies were judged to be at low risk of bias.[31 32 58] The most common limitation was lack of blinding, including in the largest trials.

Another limitation of this living systematic review and network meta-analysis is the limited quality of reporting. For some outcomes, the method in which the researchers measured and reported outcomes proved inconsistent across studies, and thus such studies could not be included in the network meta-analyses. This led the team to propose a hierarchy for the outcome mechanical ventilation, as described in the methods. Our decision to exclude treatment nodes with fewer than 100 patients or 20 events was made retrospectively because including some treatment options with small numbers of patients or events led to implausible results. We will continue to use this approach prospectively in updates of this living systematic review and network meta-analysis.

The living nature of our systematic review and network meta-analysis could conceivably (at least temporarily) amplify publication bias, because studies with promising results are more likely to be published and are published sooner than studies with negative results. The inclusion of preprints, many of which have negative results, might mediate this risk. Industry sponsored trials such as those for remdesivir and other patented drugs could be particularly at risk of publication bias, and positive results for these drugs might require more cautious interpretation than generic drugs tested in randomised controlled trials independent of industry influence. However, the inclusion of preprints in our network meta-analysis might introduce bias from simple errors and the reporting limitations of preprints. We include preprints because of the urgent need for information and because so many of the studies on covid-19 are published first as preprints.

For comparisons with sufficient data, the primary limitation of the evidence is lack of blinding, which might introduce bias through differences in co-interventions between randomisation groups. We chose to consider the treatment arms that did not receive an active experimental drug (ie, placebo or standard care) within the same node: it is possible that the unblinded standard care groups received systematically different co-interventions than groups randomised to receive a placebo. Direct comparisons in which the evidence is dominated by unblinded studies were rated down, consistent with GRADE, for risk of bias and that is reflected in the rating of the quality of evidence from the network estimate.[74] It is also possible that study level meta-analysis might not detect important subgroup modification that would otherwise be detected within trial comparisons.[75] For example, the RECOVERY trial suggested that patients with more severe disease might obtain a greater benefit from dexamethasone than patients with less severe disease.[48]

Our living systematic review and network meta-analysis is informing the development of the *BMJ* Rapid Recommendations.[6] An important difference in the methods for assessing the certainty of the evidence does, however, exist between the two. In this living systematic review and network meta-analysis, we use a minimally contextualised approach for rating the certainty of the evidence, whereas *BMJ* Rapid Recommendations uses a fully contextualised approach in which the thresholds of importance of magnitudes of effects depend on all other outcomes and factors involved in the decision.[25] The contextualisation explains potential differences in the certainty of the evidence between the two. The limitations of potentially misleading results when the network is sparse, and the desirability of focusing on direct estimates from larger studies when this is the case, explain differences in the details of the estimates of effect in this network meta-analysis and in the associated guidelines for remdesivir.[13]

To date, we are aware of two other similar efforts to ours.[76 77] We decided to proceed independently to ensure that the results fully inform clinical decision making for the associated living guidance in *BMJ* Rapid Recommendations.[6] We also include a more comprehensive search for the evidence and several differences in analytical methods, which we believe are best suited for this process. It is also important to evaluate the reproducibility and replicability of results from different scientific approaches.

We will periodically update this living systematic review and network meta-analysis. The changes from each version will be highlighted for readers and the most updated version will be the one available in the publication platform. Previous versions will be archived in the supplementary material. This living systematic review and network meta-analysis will also be accompanied by an interactive infographic and a website for users to access the most updated results in a user friendly format (magicapp.org).

Conclusions

Evidence from this living systematic review and network meta-analysis suggests that glucocorticoids probably reduce mortality and mechanical ventilation in patients with severe covid-19. Remdesivir probably reduces length of hospital stay. The effects of most drug interventions are currently highly uncertain, and no definitive evidence exists that other interventions result in important benefits and harms for any outcomes.

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Web appendix: Supplementary material